Preparation of Salicylic Acid

Salicylic acid will be prepared by a base-promoted hydrolysis, or saponification, of methyl salicylate. The product will be analyzed by melting point analysis and carbon NMR. Salicylic acid is an active metabolite of aspirin; in fact, aspirin can be thought of as a pro-drug for salicylic acid. Salicylic acid acts as anti-inflammatory and is used topically for some skin conditions, including acne. Native Americans used preparations made from the bark of the willow tree (genus Salix) for medicinal purposes. Salicylic acid is also a plant pheromone. When the structures of methyl salicylate and salicylic acid are compared, it is evident that the methoxy (OCH$_3$) group is replaced with a hydroxy (OH) group in the reaction and, thus, that salicylic acid contains one less carbon atom than does methyl salicylate and will thus have one fewer signal in its carbon NMR.

![Methyl salicylate and Salicylic acid](image)

Salicylic acid is a diprotic acid with $pK_a_1=2.98$ (Reaction 1) and $pK_a_2=13.6$ (Reaction 2). It will exist as a dianion at sufficiently high pH.

![Salicylic acid reactions](image)

The base-promoted hydrolysis of salicylic acid done in this experiment proceeds in three parts: deprotonation of the phenol hydrogen upon addition of NaOH, but before heating (Reaction 3), the actual hydrolysis and subsequent and immediate deprotonation of the salicylic acid (Reaction 4), and the protonation of the salicylic acid upon the addition of sulfuric acid (Reaction 5).

![Salicylic acid reactions](image)

Although the hydrolysis reaction itself (Reaction 4) is not studied until Chem 22, the acid-base aspects of the reaction series do pertain to Chem 21. In addition, running the reaction and isolating, purifying and analyzing the...
product provide students with the opportunity to learn useful techniques such as reflux, vacuum filtration, recrystallization, determination of melting point, and carbon NMR.

- The Role of the Laboratory (p 1)
- Learning to Do Organic Chemistry (p 41)
  - Measurements (Chapter 5), including using a syringe Pasteur pipet to measure small volumes - Figure 5.8, page 60
  - Heating (Chapter 6)
  - Microscale Reflux - Section 7.1, with apparatus in Figure 7.1b
- Intermolecular Forces in Organic Chemistry (p 127)
  - Filtration (Chapter 9 and Figure 9.7a-left)
  - Changing solubility with acid-base chemistry (Section 10.2)
  - Recrystallization (Chapter 15, with miniscale procedure in section 15.5)
  - Melting point determination (Chapter 14)
- The Spectrometric Revolution (p 309)
  - Carbon NMR (Sections 23.1 and 23.2)

**Equipment**
- Micro glassware kit
- Aluminum block or sand bath with hot plate
- Hirsch funnel and small filter flask.

**Safety**
- Methyl salicylate. Toxic. Irritant. Hazardous in case of skin contact, eye contact, or inhalation. Prolonged contact can cause target organ damage. Wear gloves.
- Sodium hydroxide. Corrosive and causes burns. Wear gloves. Let the instructor know if any is spilled.
- Salicylic acid. Irritant. Hazardous in case of skin contact, eye contact, or inhalation. Wear gloves.

**Procedure**
1. Pour 3.5 mL of water into a 10-mL round bottom flask from the micro kit. Add 0.45-0.55 grams of NaOH pellets and swirl the flask to dissolve the NaOH.
2. Weigh or tare the flask and contents (stand it up in a small beaker and include the beaker in the mass measurement or taring). Use a Pasteur pipet fitted with a 1-mL syringe to measure 0.20 mL of methyl salicylate and transfer it to the flask. Weigh again to get the mass of methyl salicylate; if you don't have at least 0.20 g, then add more and reweigh.
3. Assemble the reflux apparatus (Figure 7.1b in Techniques book)
   a. Put 1-2 boiling chips in the flask.
   b. Place a screw cap and then an o-ring over the male joint of a condenser, grease the joint, and then attach the condenser to the flask and tighten the connection to attach the two glassware pieces together securely.
   c. Place the flask in the heat source (aluminum block or sand bath on hot plate--the former is recommended), clamp the condenser to a vertical beam of the flexi-frame in the back of the fume hood with a utility clamp.
   d. Attach the water hoses. Remember that the water should always run uphill through the apparatus.
   e. Turn on the water and the heat.
4. Heat the mixture until it starts to reflux (boil). Then continue to reflux for 15 minutes. Make sure that the reflux ring doesn't get too high in the condenser as this can cause loss of material.
5. Remove the apparatus from the heat and cool to room temperature. It is OK to stick the flask in water to help cool it.
6. Remove the condenser and transfer the contents of the flask to a 25 or 50-mL beaker, leaving the boiling chips behind (or actively remove the boiling chips).
7. Get 3 mL of 3 M sulfuric acid in a 10-mL graduated cylinder. Add the sulfuric acid from the graduated cylinder in approximately 0.5-mL increments, with swirling or stirring to mix the contents after each addition. Continue to add the sulfuric acid until large quantities of solid appear and remain with swirling. The mixture should be completely opaque. Consult with the instructor if you’ve added 3 mL and this still hasn’t happened. Record the total amount of sulfuric acid used. (Neutralize the sulfuric acid in the cylinder by placing the cylinder in the sink and then adding sodium bicarbonate to it.)

8. Cool the acidified mixture in an ice-water bath to facilitate solid formation.

9. Collect the (crude) solid product by vacuum filtration with a Hirsch funnel. It is a good idea to moisten the filter paper with solvent (water in this case), start the vacuum, and then start to pour the mixture through.

10. Pour the filtrate in the inorganic waste container.

11. Weigh or tare a 10-mL Erlenmeyer flask, place the crude product in it, and reweigh to get the mass of the crude product.

12. Save a tiny amount of the crude product (enough to get a melting point, if needed). The amount of crude product that you are unable to transfer to the Erlenmeyer flask will probably be enough. This is insurance in case the recrystallization fails and you need to use the crude product for your melting point determination. If the recrystallization is successful, you won’t need the tiny amount.

13. Recrystallize the product from water in the 10-mL Erlenmeyer flask. (see Section 15.5 in Techniques book)
   a. Place a boiling stick in the flask.
   b. Add just enough water to cover the crystals (about 1 mL, unless you have a small yield of crude product) and heat the mixture to about 90°C (not quite boiling) on a hot plate. It is OK to place the flask directly on the hot plate when water is used as the recrystallizing solvent.
   c. If the crystals do not all dissolve, continue to add water in about 5-8 drop increments, heating after each addition, until the solid just dissolves. Record the total volume of water used (convert drops to mL, or start with a known volume of water in a graduated cylinder and use that as your solvent supply for the recrystallization.
   d. Remove the flask from the hot plate and the boiling stick from the mixture and allow the mixture to cool to room temperature.
   e. Then cool the flask and contents in an ice-water bath for five minutes. At this point you should have copious amounts of crystals; if not, consult with your instructor.
   f. Filter the mixture, using a clean Hirsch funnel, a clean filter flask, and a fresh piece of filter paper. Leave the vacuum on for a few minutes to pull air through the crystals to aid in drying them.
   g. Dispose of the filtrate in the inorganic waste container.

14. Transfer the crystals to a small, weighed, labeled beaker and leave them in your locker for storage until the next lab period. Water doesn’t evaporate very quickly so they will need the extra time to dry. Alternatively, you may dry them in an oven at about 100°C or using a heat lamp; however, consult with your instructor before employing either of those methods.

15. At the next lab period, weigh the salicylic acid and determine its melting point. You will also take your sample to the NMR spectrometer where an instructor will record the carbon NMR of your sample, that of another group, or a mixture of samples from different groups.

16. Cleanup summary. Filtrates go in the inorganic waste container. Boiling sticks and chips go in the container for solid waste. Melting point capillaries go either in the special waste container for them in Sci 303 or in the glass disposal. Any unused methyl salicylate goes in the organic waste container. The instructor will probably collect the salicylic acid products in a communal beaker.

**Practice Questions** (not to be turned in)

1. Suppose you are performing a recrystallization and no crystals appear, even after cooling. What should you do to attempt to get them to form? 

2. Suppose that 0.244 g of methyl salicylate was hydrolyzed, using the procedure above, and 0.188 g of purified salicylic acid was obtained. Calculate the percent yield.

3. Use the solubility chart on the following page to answer the following, based on using 0.200 g of salicylic acid in a recrystallization from water.
   a. What volume of water, in mL, is needed to dissolve that amount of salicylic acid at 60°C? If that solution is then slowly cooled down to 10°C (the solubility at that temperature is 1.3 g/L), what amount of salicylic acid remains in solution? What is the expected percent recovery of salicylic acid?
b. Repeat the calculations in part a, but using a dissolving temperature of 90°C and a final temperature of 10°C.

c. If a student used twice the volume of water necessary to just dissolve the salicylic acid at 90°C and then ultimately cooled the solution to 10°C what would be the percent recovery of salicylic acid from the recrystallization?

d. Ponder what the results of a, b and c indicate about using a larger temperature range and a smaller amount of solvent in a recrystallization. Note that this seems to be a very forgiving recrystallization.

e. In doing the calculations for parts a, b, and c, will the percent recovery change if the calculations are based on a different mass of salicylic acid?

4. Why would it not be good to use boiling water for the recrystallization of a compound with a melting point of 92°C?

5. Why is it important to weigh the methyl salicylate as opposed to using the measured volume and density to calculate the mass?

![Solubility of Salicylic Acid in Water](chart.png)